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Prognostic value of reported chest pain for cardiovascular risk stratification in primary care

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Abstract

Background: The prognostic significance of chest pain is well established in patients with coronary artery disease, but still ill defined in primary prevention. Therefore, the aim of our analysis was to assess the prognostic value of different forms of chest pain in a large cohort of primary care subjects under the conditions of contemporary modalities of care in primary prevention, including measurement of serum levels of the biomarker NT-pro-BNP.
Design: We carried out a post-hoc analysis of the prospective DETECT cohort study.
Methods: In a total of 5570 unselected subjects, free of coronary artery disease, within the 55,518 participants of the cross-sectional DETECT study, we assessed chest pain history by a comprehensive questionnaire and measured serum NT-pro-BNP levels. Three types of chest pain, which were any chest pain, exertional chest pain and classical angina, were defined. Major adverse cardiovascular events (MACEs=cardiovascular death, myocardial infarction, coronary revascularization procedures) were assessed during a 5-year follow-up period.
Results: During follow-up, 109 subjects experienced a MACE. All types of reported chest pain were associated with an approximately three-fold increased risk for the occurrence of incident MACEs, even after adjusting for cardiovascular risk factors. Any form of reported chest pain had a similar predictive value for MACEs as a one-time measurement of NT-pro-BNP. However, adding a single measurement of NT-pro-BNP and the information on chest pain resulted in reclassification of approximately 40% of subjects, when compared with risk prediction based on established cardiovascular risk factors.
Conclusions: In primary prevention, self-reported chest pain and a single measurement of NT-pro-BNP substantially improve cardiovascular risk prediction and allow for risk reclassification of approximately 40% of the subjects compared with assessing classical cardiovascular risk factors alone.

Keywords: Self-reported chest pain, NT-pro-BNP, risk prediction, primary prevention

Introduction

Coronary artery disease (CAD) is one of the most prevalent diseases and remains the leading cause of death.[1] Therefore, the identification of subjects at risk to develop CAD is a major goal in primary prevention.

In most cases, angina pectoris is a typical symptom of the initial presentation of CAD.[2] Although the significance of angina is well known in patients with a history of CAD and it is the basis for diagnostic and therapeutic decisions in clinical practice,[3–6] the prognostic value of angina as a predictor of future cardiovascular events is still ill defined in primary prevention. As the perception of angina is highly variable, especially for the elderly, women and diabetics,[7–9] its diagnostic specificity and sensitivity varies between subgroups of patients.[10,11]

Therefore, the aim of our study was to analyse the prognostic value of different types of reported chest pain in a large cohort of unselected primary care subjects under the conditions of contemporary modalities in primary prevention including measurement of the biomarker N-terminal pro-brain natriuretic peptide (NT-pro-BNP), which recently emerged as a valuable risk predictor of cardiovascular events in the general population.[12,13]

Materials and methods

The 'Diabetes Cardiovascular Risk Evaluation Targets and Essential Data for Commitment of Treatment' (DETECT) trial is a large multistage prospective longitudinal study. In brief, in the DETECT study, patients were recruited in a total of 3188 general practitioners (GPs) offices evenly distributed throughout Germany at two half-day time points. In detail, during the morning working hours (08:00–12:00) on 16 and 18 September 2003, all consecutive subjects visiting their GP for diagnostic or therapeutic counselling were recruited into the main DETECT study.[14] In total, 55,518 subjects were included into the main DETECT study addressing the demographic and cardiovascular risk profile of primary care subjects in Germany. Thus, the recruitment of all consecutive subjects visiting their primary care physician at two predefined half-days indeed represents a cross-sectional snapshot of subjects seeking medical advice with their GP throughout Germany. Of the 3188 GPs, 1000 were randomly selected to additionally obtain blood samples for standardized laboratory screening in 5–10 randomly selected subjects out of the consecutive subjects visiting the GP office at the predefined half-day recruitment period.[14] This cohort, comprising a total of 7519 subjects, was then followed-up for 5 years by their treating GP in order to document incident adverse clinical events. Importantly, the cohort of subjects with blood samples did not differ from the main 55,518 subjects of the DETECT cohort with respect to demographic and cardiovascular risk profiles, thus ascertaining recruitment of a subgroup of subjects representative for the entire study cohort, reflecting a truly unselected population.[14] For the present analysis, subjects with a history of cardiovascular disease were excluded, resulting in a study cohort of 5570 subjects, in whom clinical chemistry could be performed from blood samples obtained at inclusion into the study and correlated with 5-year clinical outcome with respect to incident adverse cardiovascular events.[14] Supplementary Table 1 illustrates the flowchart of recruitment of subjects into the present study.

Baseline examinations

Subjects completed a self-administered questionnaire, which was used to assess demographic data, smoking history, family history of coronary artery disease, information on duration and severity of cardiovascular risk factors and existing medical as well as non-medical treatment. The questionnaire included multiple-choice questions on occurrence, location and characteristics of chest pain in order to derive three definitions of chest pain (Supplementary Table 2): (1) the standardized and validated 'Rose angina',[15] which is still used by the World Health Organization (WHO) for the definition of angina and was already used in other studies;[16] (2) the clinically most frequently used 'exertional chest pain' and 'any chest pain' as well as a simple classification of chest pain proposed by the National Institute for Health and Clinical Excellence (NICE) guidelines[17] on the management of chest pain (typical angina, atypical angina and non-anginal chest pain).

Venous blood samples were immediately frozen after collection until the time of the analysis. Concentrations of plasma NT-pro-BNP was determined with a sandwich immunoassay on an ELECSYS2010 analyser (Roche diagnostics);[18] Troponin T (TnT) was measured by the Elecsys 2010, third-generation assay (F. Hoffmann-La Roche Diagnostics, Basel, Switzerland).

Established cardiovascular risk factors were defined as follows: hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90mmHg or treatment with antihypertensive medication.[19] National Cholesterol Education Program (NCEP) guidelines[20] were applied for the diagnosis of dyslipidemia. Diabetes mellitus (DM) was defined by the use of antihyperglycaemic medication or by a fasting plasma glucose level ≥126 mg/dl (7.0 mmol/l).[21] Smoking was defined as current smoking, which includes both active daily nicotine abuse and occasional active smoking. An overall risk factor score was calculated using the Framingham risk score definitions.[22]

The DETECT survey received the approval of the Ethics Committee of the Carl Gustav Carus Medical Faculty at the Technical University of Dresden (AZ: EK149092003; Date: 16 September 2003) and was registered at ClinicalTrials.gov (NCT01076608).

Endpoints

At the 5-year follow-up in 2008, state of health and medical history over the follow-up period were ascertained. The following endpoints were documented: all cause mortality, mortality of cardiovascular cause, occurrence of a myocardial infarction, and manifestation of CAD as evidenced by the necessity for coronary revascularization by either coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI). Deaths and known causes of deaths were determined by a standardized assessment form by the primary care physician and/or by the institution in which the patient was previously treated. Cardiovascular death was defined as either sudden (out-of-hospital sudden death) or myocardial infarction- related requiring documentation of myocardial infarction by hospital records. Events were verified by reviewing the hospital charts of patients with non-fatal myocardial infarction or manifestation of CAD due to the necessity for revascularization procedures. Only the first event occurring during follow-up was used as an endpoint. In addition to the individual endpoints, a combined endpoint of major adverse cardiovascular events (MACEs) was used including death from cardiovascular causes, non-fatal myocardial infarction and necessity for coronary revascularization by CABG surgery or PCI. In addition we also analysed the data excluding

revascularization as an endpoint given that reported angina might lead to invasive investigations associated with increased revascularization rates.

Statistical analyses

The association of baseline characteristics as well as the association of different definitions of chest pain with the outcome was investigated with the use of Cox proportional hazards regression. In addition to crude analysis, hazard ratios were adjusted for demographic factors (age and gender) as well as for established risk factors (arterial hypertension, diabetes mellitus, hyperlipidemia, obesity and smoking status). Estimates of the C statistic after Cox regression models (with 95% confidence intervals), which is the nonparametric estimate of the area under the receiver operating characteristic (ROC) curve, for conventional cardiovascular risk factors and NT-pro-BNP with different types of chest pain were calculated to assess model discrimination.[23]

In addition, we evaluated the ability to use different questions on chest pain as a diagnostic tool, with and without NT-pro-BNP, to reclassify risk, according to previously suggested methods.[24] Using multivariable risk models with the clinical covariates listed above, we calculated the net reclassification Improvement (NRI) and integrated discrimination improvement (IDI).[24] Subjects were reclassified based on their predicted probabilities for the future event based on the addition of chest pain diagnosis and/or biomarker concentration. The number of subjects reclassified was assessed by the category free NRI. The difference between improvement in average sensitivity and potential increase in average 'one minus specificity' was calculated be the IDI. Moreover, quantile–quantile plots were constructed in order to delineate changes in estimated risk across the entire range of risk.

Results are presented as mean (standard deviation [SD]) for approximately normal distributed variables, median (interquartile range) for skewed variables and absolute and relative frequencies for categorical variables. Two-sided p-values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were conducted with the use of STATA 11.

Results

The baseline characteristics of the study cohort and the association with MACEs are shown in Table 1. The mean age of participants at baseline was 55.6 years (SD 13.8 years; range 18–95 years). A total of 3465 participants (62.2%) were women; 1900 participants (34.1%) had arterial hypertension; 683 patients (12.3%) suffered from diabetes mellitus. Pharmacological treatment consisted of angiotensinconverting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) (23.5%), beta-blockers (20.2%), calcium channel antagonists (9.9%) or diuretics (12.4%). None of the subjects had prevalent major cardiovascular disease at baseline. During the follow-up period of 5 years, 157 participants (2.8%) died, 137 from non-cardiac causes, and 20 from cardiovascular cause. A total of 109 (2.0%) subjects experienced an incident MACE: in detail, 34 subjects suffered from non-fatal myocardial infarction and 1.5% (n=86) of the subjects underwent first revascularization procedures by PCI (n=62) or by CABG (n=24). As summarized in Table 1, the occurrence of a MACE was associated with the classical risk factors for CAD, except smoking. Likewise, subjects suffering from incident MACEs during follow-up had significantly higher NT-pro-BNP serum levels as well as a

higher incidence of elevated Troponin T (TnT) levels. However, it should be noted, that TnT levels were above the currently accepted threshold of >0.01 pg/dl in only 0.4% of the entire study cohort, thus precluding its use as a clinically meaningful biomarker in primary prevention.

All types of reported chest pain, Rose angina, exertional chest pain and any chest pain, as well as all NICE angina classifications were associated with an approximately three-fold increased risk for the occurrence of MACE (Table 2).[15,17] These associations remained unchanged after adjustment for age and gender or after additional adjustment for established cardiovascular risk factors. Most importantly, exclusion of revascularization from the combined MACE endpoint did not alter the results (Table 2), thus documenting that the observed associations between different types of reported chest pain and adverse outcome not exclusively driven by a higher likelihood of patients with chest pain undergo invasive investigations leading to an increased rate of revascularization. None of the types of chest pain increased the hazard ratios for all-cause mortality.

As illustrated in Supplementary Table 3, all definitions of reported chest pain were associated with a higher prevalence of established cardiovascular risk factors.

The C statistic for Cox regression models increased significantly for the prediction of major cardiovascular events, when all types of reported chest pain were separately incorporated into a model with the established cardiovascular risk factors (Table 3 and Supplementary Table 5), with Rose angina achieving only borderline significance. Moreover, when adding the combination of different types of chest pain and NT-pro-BNP to cardiovascular risk factors into the risk prediction model, a further significant increase of the C statistics for Cox regression models predicting MACEs was observed for all definitions of chest pain. Importantly, as summarized in Supplementary Table 6, the addition of NT-pro-BNP serum levels specifically increased the C statistics for all forms of NICE angina, whereas no added value was observed in subjects without angina.

Finally, we tested the usefulness of adding chest pain, alone and in combination with NT-pro-BNP serum levels, to conventional cardiovascular risk factors by assessing the number of participants reclassified and calculating the IDI on top of the Framingham 10-year risk prediction of a major cardiovascular event. As summarized in Table 4, integrated discrimination was significantly improved for major cardiovascular events, when all types of self-reported chest pain were incorporated into the risk model. Reclassification effect by adding the data on exertional chest pain was similar to measuring NT-pro-BNP serum levels (Table 4a).

Most importantly, however, combining data on self-reported chest pain and NT-pro-BNP serum levels resulted in a further significant improvement of integrated discrimination (Table 4b). In fact, approximately 40% of the subjects were reclassified either into a higher risk category for subjects with events or into a lower risk category in subjects without events. The incremental value of adding self-reported chest pain to conventional risk factors for improved risk prediction is also illustrated by the quantile–quantile plots shown in Figure 1, which demonstrate significant deviations from the line of identity indicating changes in estimated risk across the continuum of risk estimates for all types of chest pain.

Discussion

The results of the present study demonstrate that in a contemporary nationwide, cross-sectional sample of primary care subjects, free of any evidence of CAD, all types of reported chest pain are associated with an approximately three-fold increase in risk for subsequent MACEs during a 5-year follow-up period. Importantly, the predictive power of reporting any form of chest pain was similar to the risk predictive value of measuring NT-pro-BNP serum levels. However, adding the information on chest pain, and a single measurement of NT-pro-BNP serum levels resulted in reclassification of approximately 40% of primary care subjects when compared with risk prediction based on established cardiovascular risk factors.

The prognostic significance of angina is well established in patients with established CAD. However, the few prognostic studies of angina in primary care provided inconclusive results.[25] A recent study including 1785 subjects with a diagnosis of self-reported angina as their first manifestation of ischaemic heart disease demonstrated that men with angina are at significantly increased risk of suffering from major adverse cardiovascular events including death, acute myocardial infarction and revascularization procedures.[26] The present approximately three-fold larger study not only extends these observations, but also reveals that various forms of reported angina provided similar incremental predictive information compared with measuring NT-pro-BNP serum levels. Thus, a simple question regarding the presence or absence of angina appears to provide predictive information as robust as NT-pro-BNP in this setting.

While recent years have witnessed great enthusiasm to use biomarkers as tools to enhance risk prediction in primary prevention populations,[12,13,27,28] the incremental value of a variety of tested biomarkers to enhance risk prediction in primary prevention turned out to be rather small and resulted in only small, if any, improvement in discrimination and reclassification.[28] Nevertheless, consistent throughout most of the studies, NT-pro-BNP serum levels demonstrated the greatest prognostic value in primary prevention subjects.[12,13,27,29–31] The results of the present study confirm the utility of NT-pro-BNP as a biomarker for population screening. However, importantly, the incremental value of measuring NT-pro-BNP serum levels for cardiovascular risk prediction in primary prevention was restricted to subjects reporting angina.

Thus, adding NT-pro-BNP and all types of angina to established risk factors led to a further significant improvement in integrated discrimination. Thus, a simple question regarding any type of chest pain, combined with a single measurement of NT-pro-BNP serum levels results in reclassification of 5-year predicted risk of approximately 40% of subjects compared with the assessment of classical risk factors alone, providing indeed a time-efficient and feasible strategy for risk assessment in primary prevention (Figure 2).

Limitations

The definitions of self-reported angina included previously validated conventional categorization of chest pain, such as Rose angina[15] as well as the simple NICE guidelines[17] recommended classification, in order to allow for generalization of the results. Thus, we cannot rule out that more sophisticated questioning by the primary physician for more precise differentiation between the various forms of chest pain would have had an impact on the results. However, with respect to time constraints and immense workload in primary care physician practices, a time-efficient, standardized questionnaire of self-reported angina appears to be sufficient to effectively improve risk prediction, as demonstrated by the results of the present study. By design, the present study does not allow for the distinction between prevalent and incident cases of chest pain, as no data were obtained regarding the duration of

chest pain symptoms. Diagnostic work-up and management of subjects with chronic chest pain (prevalent cases) may in fact have led to an underestimation of the observed association with MACEs. However, the results of our analyses did not change when excluding the necessity for revascularization as an endpoint. Thus, eliminating the 'self-fulfilling-prophecy' that subjects with incident chest pain will be more likely to undergo invasive coronary diagnostic work-up resulting in an increased incidence of revascularization procedures demonstrated, that the results of the present study are not exclusively driven by the lack of differentiation between incident and prevalent cases of angina. Furthermore in line with the general office hours of GPs in Germany, subjects were recruited during the morning hours. This may have a potential selection bias into the DETECT cohort.

Albeit rather small, the relative number of cardiovascular events in the present study with a 5-year follow-up period is essentially identical to data from recently published European population-based studies in primary prevention,[33] suggesting the usefulness of the DETECT cohort for cardiovascular risk estimation in a primary prevention population free of CAD.

In summary, the present study is the first to validate self-reported chest pain as a useful tool to enhance cardiovascular risk prediction in primary care subjects, given the simplicity of retrieving information on chest pain in combination with a single measurement of NT-pro-BNP for risk assessment in primary care.

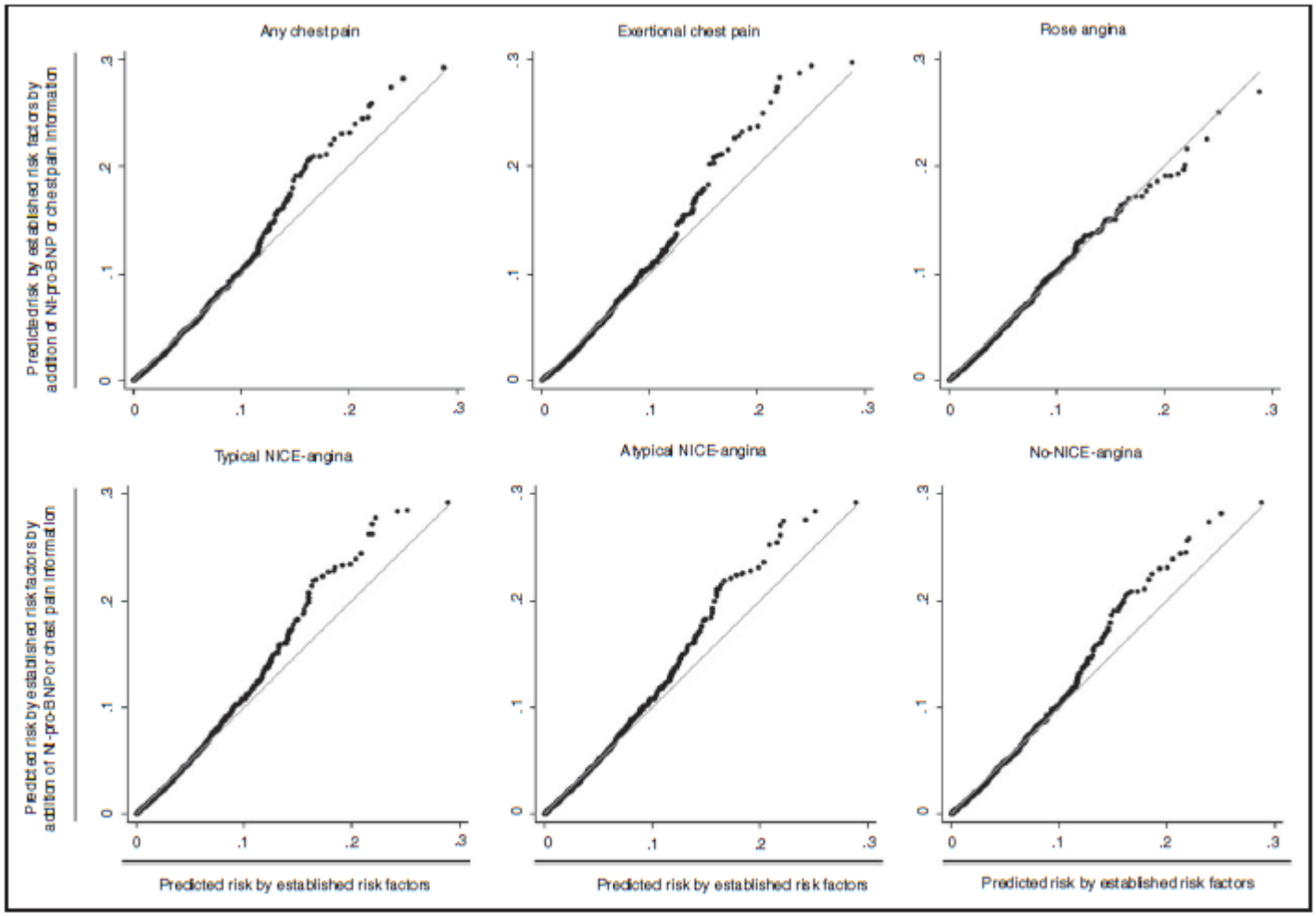

Figure 1. (a) Quantile–quantile plots of change in estimated risk for occurrence of major adverse cardiovascular events (MACEs) by addition of chest pain information. Established risk factors are: systolic and diastolic blood pressure, smoking status, hyperlipidemia, diabetes mellitus, obesity and age. (b) Quantile–quantile plots of change in estimated risk for occurrence of MACEs by addition of chest pain information and NT-pro-BNP. Established risk factors are: systolic and diastolic blood pressure, smoking status, hyperlipidemia, diabetes mellitus, obesity and age. NT-pro-BNP denotes N-terminal pro brain natriuretic peptide. For risk stratification by NT-pro-BNP the study-specific optimal cut-off was used (>121.9 mg/dl).

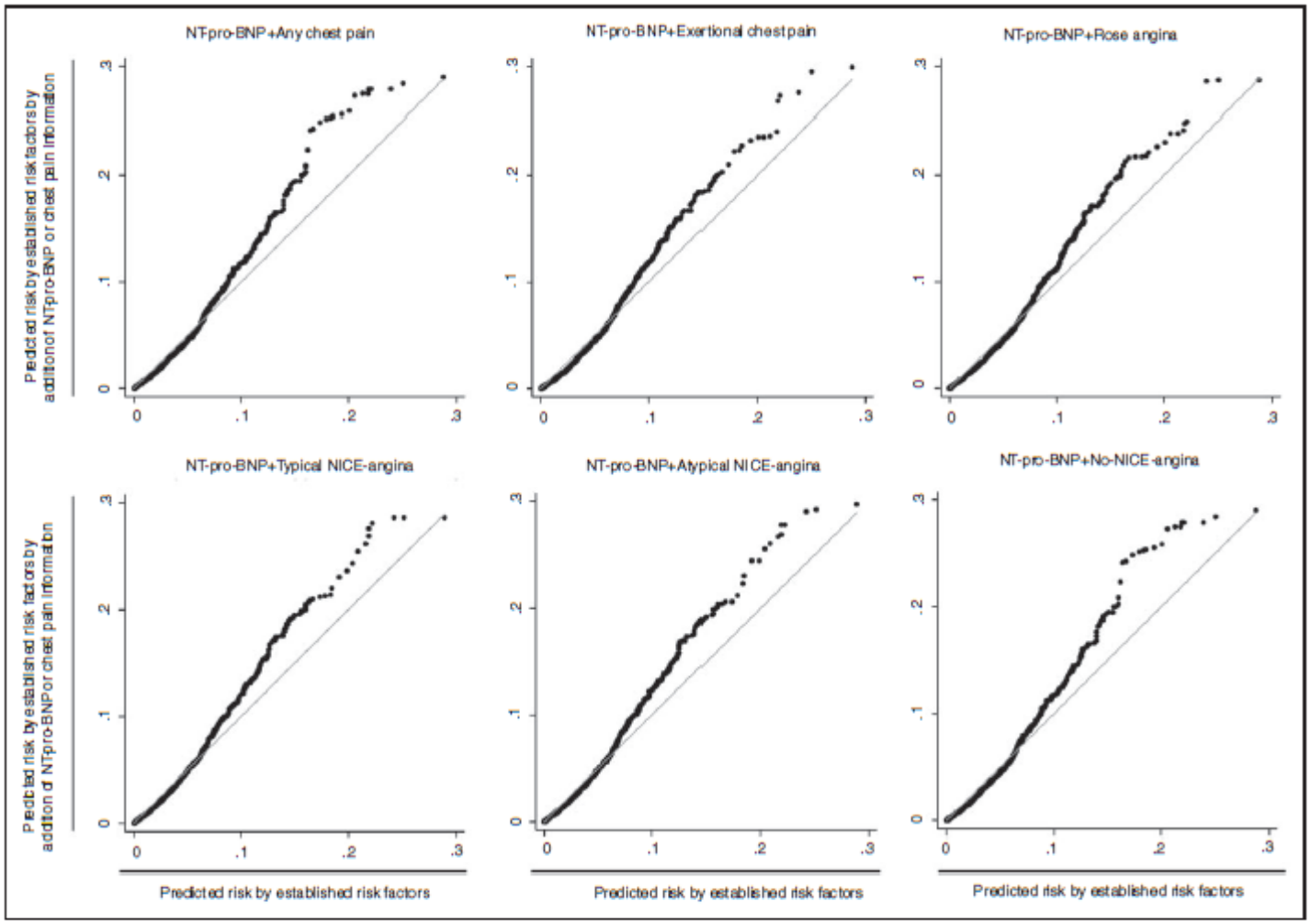

Figure 1. Continued.

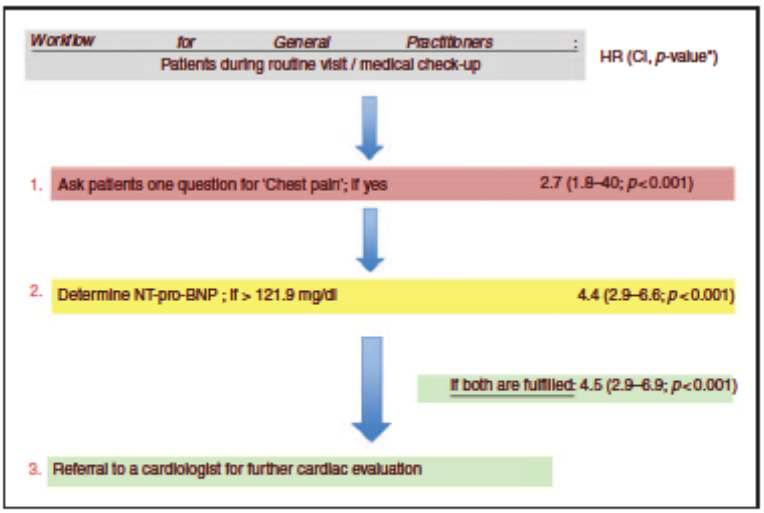

Figure 2. Algorithm for simple risk stratification in general practitioners office with risk stratification by asking one question for occurrence of chest pain and measuring NT-pro-BNP. NT-pro-BNP denotes N-terminal pro brain natriuretic peptide. For risk stratification by NT-pro-BNP the study-specific optimal cut-off was used (>121.9 mg/dl); (*) HR=Hazard ratio for occurance of major cardiovascular event (MACE) within five years; CI=Confidence interval.

Table 1. Baseline characteristics and association with incident MACEs

Characteristics	Total[2]	None-MACE[2]	MACE[2]	HR[1] (95%CI); p-value
Age, mean (SD), years[5]	55.6 (13.8)	55.4 (13.7)	68.1 (10.5)	1.08 (1.06–1.10); p < 0.001
Female, *n* (%)	3465 (62.2)	3429 (62.8)	36 (33.0)	3.40 (2.28–5.07); p < 0.001
Hypertension, *n* (%)	1900 (34.1)	1824 (33.4)	76 (69.7)	4.43 (2.94–6.66); p < 0.001
Systolic blood pressure, mean(SD), mmHg[6]	131.5 (18.1)	131.4 (18.2)	139.8 (16.0)	1.02 (1.02–1.03); p < 0.001
Diastolic blood pressure, mean(SD), mmHg[6]	80.1 (9.8)	80.1 (9.8)	81.4 (10.0)	1.01 (1.00–1.03); p < 0.135
Antihypertensive treatment, *n* (%)	1660 (31.5)	1589 (30.7)	71 (69.6)	2.80 (1.76–4.45); p < 0.001
ACEI or ARB, *n* (%)	1307 (23.5)	1247 (22.8)	60 (50.1)	3.99 (2.74–5.83); p < 0.001
Beta-blocker, *n* (%)	1068 (20.2)	1030 (19.9)	38 (37.3)	1.32 (0.87–1.98); p < 0.189
Antagonist of calcium, *n* (%)	524 (9.9)	492 (9.5)	32 (31.4)	2.65 (1.73–4.05); p < 0.001
Diuretics, *n* (%)	654 (12.4)	631 (12.2)	23 (22.6)	1.24 (0.77–1.98); p < 0.375
Diabetes mellitus, *n* (%)	683 (12.3)	654 (12.0)	29 (26.6)	2.60 (1.70–3.98); p < 0.001
Fasting plasma glucose, mean (SD), mg/dl[7]	99.4 (32.8)	99.1 (32.4)	116.4 (43.4)	1.01 (1.01–1.01); p < 0.001
HbA1c, mean (SD), %	5.5 (0.8)	5.5 (0.8)	5.9 (0.9)	1.50 (1.36–1.66); p < 0.001
Oral drug treatment, *n* (%)	436 (8.3)	415 (8.0)	21 (20.6)	1.87 (1.15–3.04); p < 0.011
Insulin treatment, *n* (%)	187 (3.5)	179 (3.5)	8 (7.8)	1.53 (0.74–3.16); p < 0.254
Hyperlipidemia, *n* (%)	1552 (27.9)	1501 (27.5)	51 (46.8)	2.26 (1.55–3.29); p < 0.001
Statins, *n* (%)	570 (10.8)	546 (10.6)	24 (23.5)	1.62 (1.02–2.57); p < 0.042
Other lipid lowering drugs, *n* (%)	154 (2.9)	147 (2.8)	7 (6.9)	1.64 (0.76–3.53); p < 0.209
Total cholesterol, mean(SD), mg/dl[7]	225.8 (42.3)	225.8 (42.2)	229.1 (46.1)	1.00 (1.00–1.01); p < 0.415
HDL cholesterol, mean(SD), mg/dl[7]	55.8 (18.6)	56.0 (18.6)	47.9 (17.4)	0.97 (0.96–0.99); p < 0.001
LDL cholesterol, mean(SD), mg/dl[7]	129.3 (33.4)	129.2 (33.3)	131.9 (35.8)	1.00 (1.00–1.01); p < 0.404
Current smoker, *n* (%)	1097 (21.3)	1078 (21.4)	19 (19.6)	0.91 (0.55–1.49); p < 0.709
Ex-smoker, *n* (%)	1254 (24.4)	1224 (24.3)	30 (30.9)	1.28 (0.84–1.95); p < 0.252
Family history of CAD, *n* (%)	804 (14.9)	790 (15.0)	14 (13.3)	0.94 (0.72–1.22); p < 0.653
Hip-to-waist ratio, mean (SD)	1.13 (0.13)	1.13 (0.13)	1.07 (0.10)	0.04 (0.01–0.12); p < 0.001
Body mass index, mean (SD), kg/m^2	26.9 (4.8)	26.9 (4.8)	28.1 (4.5)	1.05 (1.02–1.08); p < 0.001
Framingham Score-predicted risk, mean (SD)	10.2 (10.5)	10.2 (10.5)	20.6 (9.9)	1.08 (1.07–1.12); p < 0.001
Biomarkers				
NT-pro-BNP[3], median (interquartile range), pg/ml	57.6 (29.0–115.1)	115.1 (291.7)	375.5 (592.2)	4.39 (2.92–6.61); p < 0.001
Troponin T[4], mean (SD), pg/dl	0.01 (0.01)	0.01 (0.00)	0.02 (0.04)	1.22 (1.17–1.28); p < 0.001
Creatinine, mean (SD), mg/dl	1.20 (0.22)	1.19 (0.21)	1.30 (0.47)	2.73 (1.86–4.02); p < 0.001

MACE, major cardiovascular event including death from cardiovascular causes, non-fatal myocardial infarction or necessary revascularization by PCI or CABG; HR, hazard ratio; CI, confidence interval; SD, standard deviation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; CAD, coronary artery disease; [1]Hazard ratio for increase of one unit if not otherwise stated. [2]All percentages refer to number of subjects with existing data. [3]HR for NT-pro-BNP above 121.9 pg/ml. [4]HR for an increase of 0.01 pg/dl. [5]HR for an increase of 10 years. [6]HR for an increase of 5 mmHg. [7]HR for an increase of 10 mg/dl.

Table 2. Hazard ratios for death by all causes, death by cardiovascular cause/non-fatal myocardial infarction and incident major cardiovascular events (MACE), according to definition of chest pain

	Death by all causes ($n=137$)		Death by cardiovascular cause/non-fatal myocardial infarction ($n=54$)		MACE ($n=109$)	
	HR (95% CI)	*p*–value	HR (95% CI)	*p*–value	HR (95% CI)	*p*–value
Any chest pain (n=1463)						
Crude	1.10 (0.74–1.62)	0.648	2.17 (1.23–3.83)	0.007	2.70 (1.82–4.01)	<0.001
Adjusted ($^{+}$)	0.97 (0.66–1.44)	0.885	2.12 (1.20–3.74)	0.010	2.68 (1.79–4.00)	<0.001
Adjusted ($^{++}$)	1.02 (0.69–1.52)	0.907	2.23 (1.26–3.94)	0.006	2.71 (1.82–4.04)	<0.001
Exertional chest pain (n=1003)						
Crude	1.47 (0.98–2.22)	0.063	3.03 (1.71–5.37)	<0.001	3.36 (2.25–5.00)	<0.001
Adjusted ($^{+}$)	1.23 (0.81–1.86)	0.337	2.90 (1.62–5.19)	<0.001	3.28 (2.17–4.96)	<0.001
Adjusted ($^{++}$)	1.26 (0.83–1.91)	0.274	2.87 (1.60–5.13)	<0.001	3.19 (2.12–4.82)	<0.001
Rose angina[15] ($n=547$)						
Crude	1.29 (0.76–2.18)	0.344	2.82 (1.46–5.43)	0.002	2.78 (1.75–4.41)	<0.001
Adjusted ($^{+}$)	1.14 (0.66–1.95)	0.645	2.96 (1.51–5.82)	0.002	2.97 (1.82–4.84)	<0.001
Adjusted ($^{++}$)	1.16 (0.68–1.99)	0.589	2.93 (1.50–5.76)	0.002	2.95 (1.81–4.82)	<0.001
NICE angina classification[17]						
Typical NICE angina ($n=1072$)						
Crude	1.19 (0.79–1.78)	0.408	2.50 (1.44–4.34)	0.001	3.15 (2.15–4.61)	<0.001
Adjusted ($^{+}$)	1.07 (0.71–1.61)	0.746	2.44 (1.40–4.26)	0.002	3.18 (2.16–4.69)	<0.001
Adjusted ($^{++}$)	1.11 (0.74–1.66)	0.620	2.40 (1.38–4.16)	0.002	3.14 (2.13–4.63)	<0.001
Atypical NICE angina ($n=1115$)						
Crude	1.23 (0.83–1.82)	0.311	2.38 (1.37–4.13)	0.002	3.00 (2.05–4.38)	<0.001
Adjusted ($^{+}$)	1.11 (0.75–1.66)	0.598	2.34 (1.34–4.08)	0.003	3.05 (2.07–4.49)	<0.001
Adjusted ($^{++}$)	1.15 (0.78–1.71)	0.474	2.28 (1.31–3.95)	0.003	3.00 (2.03–4.43)	<0.001
No NICE angina ($n=1463$)						
Crude	1.10 (0.74–1.62)	0.648	2.17 (1.23–3.83)	0.007	2.70 (1.82–4.01)	<0.001
Adjusted ($^{+}$)	0.97 (0.66–1.44)	0.885	2.12 (1.20–3.74)	0.010	2.68 (1.79–4.00)	<0.001
Adjusted ($^{++}$)	1.02 (0.69–1.52)	0.907	2.23 (1.26–3.94)	0.006	2.71 (1.82–4.04)	<0.001

HR, hazard ratio; CI, confidence interval; ($^{+}$) = Data were adjusted for the following variables: age at baseline (continuous) and gender (binary). ($^{++}$) = Data were adjusted for the following variables: age at baseline (continuous), gender (binary), smoking status (binary), hypertension (binary), hyperlipidemia (binary), obesity (binary) and diabetes (binary).

Table 3. C-statistics for Cox-regression models based on different definitions of chest pain and the addition of NT-pro-BNP for predicting incident major cardiovascular events (MACEs)

	MACE	
	C statistics (+)	*p-value* (+)
Any chest pain		
Established risk factors(*)	0.774	Reference model
'Any chest pain'	0.632	–
NT-pro-BNP (**)	0.672	–
Established risk factors(*) plus 'Any chest pain'	0.806	–
Estimated difference with the addition of 'Any chest pain'	0.025	0.024
Established risk factors(*) plus 'Any chest pain' and NT-pro-BNP (**)	0.824	–
Estimated difference with the addition of 'Any chest pain' and NT-pro-BNP (**)	0.043	0.003
Exertional chest pain		
Established risk factors(*)	0.774	Reference model
'Exertional chest pain'	0.647	——
NT-pro-BNP (**)	0.672	–
Established risk factors(*) plus 'Exertional chest pain'	0.812	–
Estimated difference with the addition of 'Exertional chest pain'	0.034	0.012
Established risk factors(*) plus 'Exertional chest pain' and NT-pro-BNP (**)	0.830	–
Estimated difference with the addition of 'Exertional chest pain' and NT-pro-BNP (**)	0.048	0.003
Rose angina[15]		
Established risk factors(*)	0.774	Reference model
'Rose angina'	0.579	–
Nt-pro-BNP (**)	0.672	–
Established risk factors(*) plus 'Rose angina'	0.798	–
Estimated difference with the addition of 'Rose angina'	0.020	0.054
Established risk factors(*) plus 'Rose angina' and NT-pro-BNP (**)	0.814	–
Estimated difference with the addition of 'Rose angina' and NT-pro-BNP (**)	0.036	0.007

NT-pro-BNP, N-terminal pro-brain natriuretic peptide. (*) = Established risk factors: systolic blood pressure, diastolic blood pressure, smoking status, hyperlipidemia, diabetes mellitus, obesity and age. (**) = NT-pro-BNP > 121.9 mg/dl (= study-specific optimal cut-off derived from receiver operating characteristic analysis)). (+) = Only determined for subjects with complete data on established risk factors and NT-pro-BNP measurement ($n = 4734$).

Table 4a. IDI of 5-year predicted risk for occurrence of major cardiovascular events (MACEs) by addition of chest pain information or NT-pro-BNP

	IDI % (p–value)	Relative change in higher risk category for cases and lower risk category in non-cases (%)
Any chest pain	0.65 (0.049)	15.3
Exertional chest pain	0.96 (0.029)	20.9
Rose angina[15]	0.68 (0.049)	15.7
Typical NICE Angina[17]	0.92 (0.013)	19.8
Atypical NICA Angina[17]	0.81 (0.019)	18.7
No NICE Angina[17]	0.65 (0.049)	15.3
NT-pro-BNP	1.13 (0.001)	20.8

NRI, net reclassification improvement; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; IDI, integrated discrimination improvement (difference of averaged improvement in sensitivity and averaged increase in 1-specificity); NT-pro-BNP, N-terminal pro-brain natriuretic peptide >121.9 mg/dl (=study-specific optimal cut-off derived from receiver operating characteristic analysis).

Table 4b. IDI of 5-year predicted risk for occurrence of MACEs by addition of chest pain information and NT-pro-BNP

	IDI* % (p–value)	Relative change in higher risk category for cases and lower risk category in non-cases (%)
Any chest pain + NT-pro-BNP	2.04 (< 0.001)	40.7
Exertional chest pain + NT-pro-BNP	2.47 (<0.001)	48.5
Rose angina[15] + NT-pro-BNP	2.11 (<0.001)	42.1
Typical NICE Angina[17] + NT-pro-BNP	2.11 (<0.001)	42.1
Atypical NICE Angina[17] + NT-pro-BNP	1.99 (<0.001)	36.5
No NICE Angina[17] + NT-pro-BNP	2.04 (<0.001)	40.7

NRI, net reclassification improvement; IDI, integrated discrimination improvement (difference of averaged improvement in sensitivity and averaged increase in 1-specificity); NT-pro-BNP, N-terminal pro-brain natriuretic peptide > 121.9 mg/dl (= study-specific optimal cut-off derived from receiver operating characteristic analysis); *Only determined for subjects with complete data on established risk factors and NT-pro-BNP measurement (n = 4734).

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Conflict of interest

None of the authors have any conflict of interest pertaining to the data presented, or have published or submitted any related papers from the same study.

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